Draft Guidance for Industry and FDA Staff

PROCEDURES FOR HANDLING POST-APPROVAL STUDIES IMPOSED BY PMA ORDER

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: September 15, 2005

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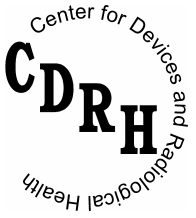
For questions regarding this document contact Steven H. Chasin, Ph.D., Deputy, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, 301-594-3674.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Postmarket Surveillance
Office of Surveillance and Biometrics

Preface

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Draft Guidance for Industry and FDA Staff

PROCEDURES FOR HANDLING POST-APPROVAL STUDIES IMPOSED BY PMA ORDER

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

Evaluation of Premarket Approval Applications (PMAs) by the Center for Devices and Radiological Health (CDRH or Center) is a multi-step process in which the Center evaluates the sponsor's information to reach the final decision on whether a product can be approved. To help assure the continued safety and effectiveness of an approved device, CDRH sometimes requires post-approval studies (these have sometimes been referred to as Condition of Approval or Post-Approval studies) under 21 C.F.R. 814.82(a)(2), which states:

> Post-approval requirements may include as a condition to approval of the device: **Continuing evaluation and periodic reporting** on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted.

Congress recognized the value of post-market controls in the Food and Drug Administration Modernization Act of 1997 (FDAMA), which added section 513(a)(3)(C) to the Act. Section 513(a)(3)(C) provides:

> In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 515 has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.

Thus, post-market controls, including post-approval studies, are a valuable tool in striking a balance between requiring the least burdensome evidence to support premarket approval and assuring continued product safety and effectiveness through real-world and long-term follow-up of marketed devices.

Our goal in this guidance is to provide recommendations to sponsors and CDRH staff on expectations concerning format, content, and review of reports related to post-approval studies imposed by PMA order to help ensure they are conducted effectively and efficiently, and in a least burdensome manner. Although some post-approval studies may involve animal or laboratory bench studies, the recommendations in this draft guidance focus on **clinical post-approval studies**. We intend for these recommendations to improve post-approval studies by:

- helping the Center and sponsors assure clear and consistent data from all sponsors;
- helping us easily and quickly identify and **track** post-approval studies;
- enhancing sponsor and FDA discussions on mutually understood study objectives;
- facilitating timely discourse on study issues and challenges; and
- providing opportunities to resolve issues.

In sum, these improvements are intended to enhance postmarket safety by ensuring that appropriate post-approval studies are efficiently initiated, completed, and reviewed.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Background

The last few years have seen more attention focused on post-approval studies for FDA-regulated products. A 1996 HHS Office of Inspector General (OIG) study questioned the effectiveness of

the Center for Drug Evaluation and Research's (CDER) ability to track post marketing studies[1]. In the 1997 FDAMA legislation, Congress imposed certain requirements on post-market studies of drugs (section 506B (21 U.S.C. 356b)). In response, CDER and the Center for Biological Evaluation and Research (CBER) post on CDER's website http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm the status of certain post marketing studies. Regarding medical devices, the Institute of Medicine has initiated a study that, among its other objectives, will focus on our ability to use post-approval studies as an effective postmarket surveillance tool.

CDRH also initiated an internal review to evaluate its ability to monitor post-approval studies. As a result of that review we have:

- expanded consultation between the Office of Device Evaluation (ODE) and the Office of Surveillance and Biometrics (OSB) on designing post-approval studies;
- developed a new post-approval study computer tracking system;
- shifted the responsibility for monitoring the progress and results of post-approval studies from the premarket staff, ODE, to the postmarket staff, OSB;
- established a joint ODE-OSB task force to evaluate and recommend methods to improve the quality and completion of post-approval studies; and
- determined appropriate public notification and enforcement options concerning post-approval studies.

These actions are intended to ensure that:

- sponsors produce post-approval studies that use good science and high quality methodology in the study design;
- sponsors provide study results at agreed-upon intervals;
- CDRH provides timely and accurate notification to sponsors regarding their study status; and
- CDRH provides appropriate public notification of study information and, when necessary, undertakes withdrawal proceedings in accordance with section 515(e) of the Act.

Purpose of the Guidance

[1]Postmarketing Studies of Prescription Drugs. Department of Health and Human Services, Office of Inspector General Final Report, May 1996.

The draft guidance has two purposes. First, it is designed to aid sponsors who are subject to post-approval study requirements imposed by PMA order by providing specific recommendations on the information they should include when submitting their post-approval protocols and study results.

Second, the draft guidance is intended to increase the transparency of CDRH's approach to post-approval study requirements. The guidance discusses CDRH's plan to inform stakeholders of the status of post-approval studies by posting the status on the Internet.[2] In addition, the guidance discusses opportunities for sponsors and CDRH staff to present the status of post-approval studies during the public meetings of the Advisory Panels that may have recommended approving the device with a condition that the sponsor conduct a post-approval study.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to the procedures for handling post-approval studies and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether a less burdensome approach exists or other matters related to this guidance document, please submit your comments as indicated on the cover of this document.

Definitions of Terms Used in Reporting Post-Approval Studies

We recommend that in reporting the status of post-approval studies sponsors understand and use the following terms:

Post-Approval Study is a clinical study or other investigation, usually conducted under a single protocol and included in the PMA order, to gather specific information to address precise study objectives about an approved medical device.

Post-Approval Study Commitment is an agreement by the sponsor and confirmed by us in writing to conduct one or more studies to provide additional information concerning the approved medical device. A post-approval study commitment will usually consist of one study, i.e., the completion of a single study will fulfill that post-approval study commitment.

Interim Study Status Reports are reports to CDRH on the status of the post-approval study prior to its completion. An interim study status report should be submitted every six months for the first two years of the study and annually thereafter until the time a Final Study Report has been submitted. You should use one of the terms below to describe the status of the study in the interim reports. These terms will also be used on the FDA web page to describe the study status.

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[2] As noted earlier, CDER and CBER already provide similar information on their websites.

- Pending: The study has not begun (i.e., no subjects have been enrolled), but the projected date for completing patient accrual has not passed. If the study has not been initiated by the projected date for completion of patient enrollment, you should categorize the study as Delayed.
- On-going: The study is proceeding according to, or is ahead of, the original schedule. A study is on-going as long as the activities are proceeding according to the original schedule and until a final study report is submitted to and accepted by us.
- Delayed: The study is delayed when either 1) it is proceeding but is behind the original schedule or 2) we have not received the **interim** report within one month of its due date. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the interim or final report. The original schedule, which is typically stated in the PMA order, serves as the basis for defining a study as Delayed.
- Terminated: You have ended the study before completion, do not intend to finish the study as it was originally designed, and have not submitted a final study report.
- Submitted: You have concluded or terminated the study, and submitted a final study report, but we have not advised you that you met the study commitment.
- Completed: You have submitted and we have accepted the final study report.

When Should Sponsors Submit Post-Approval Study Protocols?

The final protocol for a post-approval study and the schedule for study completion are based upon agreements reached between CDRH and you. Generally, we will ask for and you should submit protocols prior to PMA approval. If a protocol is not agreed upon prior to the device approval, you should submit the protocol as a PMA supplement within an agreed upon timeframe and clearly label it Post-approval Study Protocol. In addition, you will generally be ordered to submit study status reports, as discussed later in this guidance.

What Will Happen if the Sponsor and CDRH Cannot Agree on a Protocol?

As discussed earlier, we developed this draft guidance to help facilitate timely discussions with sponsors on study issues and challenges. We believe that early and on-going interactions with sponsors will minimize any disagreements on protocols or other study issues and will be the primary method for resolving any issues. However, if concerns remain unresolved or a sponsor does not comply with post-approval study requirements, other actions may be necessary. In appropriate instances, the agency has authority to order postmarket surveillance under section 522 of the act (21 C.F.R. part 822) and, where the legal criteria are met, to withdraw approval of the PMA

under section 515(e) of the act (21 C.F.R. 814.46(a)). In addition, a significant or knowing failure to report information about a post-approval study, or where such failure constitutes a risk to public health, may result in civil money penalties.

What Should the Post-Approval Study Status Report Include?

The Center's ability to **track** and **evaluate** post-approval depends upon the quality and timeliness of information provided by the sponsor. The recommendations in this section are intended to ensure that the reports you submit contain enough information for us to identify the sponsor, product being studied, specific study being conducted, status of the study and the reasons, if any, for delays or failures to complete the study. We believe the data elements below will allow us to provide you with timely and effective feedback.

We recommend that you provide the information listed below for each post-approval study submitted under 21 C.F.R. 814.82(a)(2). When more than one study is being conducted to respond to a single commitment, you should list appropriate information for each study separately. We recommend that your post-approval study reports provide the following information, clearly identified and in separate sections when you submit your reports:

Section I: General Information: We recommend this section contain the following information:

- Sponsor Name and Information: The name of the individual or entity holding the approved PMA.
    - Company Name/Institution Name
    - Establishment Registration Number
    - Division Name (if applicable)
    - Phone Number (include area code)
    - Fax Number (include area code)
    - Street Address
    - City
    - State/Province
    - Zip/Postal Code
    - Contact name and title
    - Contact e-mail address

- Submission Correspondent information (if different from Sponsor) should contain:
    - Company Name/Institution Name
    - Phone Number (include area code)
    - Fax Number (include area code)

  - Street Address
  - City
  - State/Province
  - Zip/Postal Code
  - Contact name and title
  - Contact e-mail address

- Product Name: The approved product's established name and proprietary name. If the product is distributed under more than one proprietary name, you should include all proprietary names.
- Model Number
- Application Number: The PMA number and supplement number, if any, for which the post-approval commitment was made.
- Date of PMA approval: The date the PMA or PMA supplement was first approved for marketing in the United States for which the post-approval study is required under 21 C.F.R. 814.82(a). This date will appear on the approval letter for the original application.
- Date of Post-approval Study Commitment: For study commitments made before or at the time of approval of an original application or supplemental application, this date is the same as the date of FDA's approval of the original application or supplemental application. For commitments finalized after approval, this is the date of FDA's letter confirming the commitment.
- Phone Number (include area code)
- Fax Number (include area code)
- Street Address
- City
- State/Province
- Country
- Zip/Postal Code
- Contact name and title
- Contact e-mail address

Section II: Submission Information: We recommend this section contain the following information:

- Date of Submission
- Data included in this submission (choose one):
  - Clinical Studies,
  - Animal Studies.

- Type of Submission: (Choose one)
  - Postmarket Study Protocol,
  - Postmarket Study Protocol Revision,
  - Postmarket Study Interim Report, or
  - Postmarket Study Final Report.

  - Response to FDA Correspondence Concerning
    - Deficient Study Protocol,
    - Deficient Interim Report,
    - Deficient Final Report, or
    - Other Reason (specify).
- Interim Study status (see Definitions of Terms used in Reporting Post-Approval Studies):
  - Pending,
  - On-going,
  - Delayed,
  - Terminated, or
  - Submitted.

Section III: Study Information: We recommend this section contain the following information (as applicable):

- Purpose of the study, including study goals and objectives.
- Patient population being studied, including specific illness or condition and whether the study targets subpopulations such as pediatric or geriatrics, the total number of subjects to be studied and length of patient follow-up.
- Original schedule for conducting study, date CDRH and you agreed to the schedule, and the date for completing and reporting the post-approval study commitment. This is the original schedule established by CDRH and you. We recognize that study phases may vary depending on the type and design of the study. However, in conducting a study, certain milestones are common and important to determine the study progress. These are:
  - study start date,
  - date of submitting the study protocol to us,
  - patient accrual start date,
  - total patient accrual completion to date,
  - total patient accrual rate to date: You should provide the number of patients that have been enrolled to date and the total planned enrollment for the study.
  - study targets: percentage of patients reaching each designated study phase,
  - anticipated study completion date,
  - submission of interim study report date, and
  - submission of the final study report date
- To the extent necessary, you should explain the particular status category
- Revised schedule, if the study schedule has changed since your last report.
- Explanation for the basis for the revision of the study schedule. You should explain, in detail, the causes for delays and your plan(s) to address the obstacle(s) to continue the study.
- Summary data and interpretation of study results to date.

You should provide the projected dates for phases of the study in the original schedule that you submitted to us. In addition, if the study commitment includes reporting intermediate milestones (e.g., evaluation of surrogate endpoints in a study that also measures clinical benefits), you should

include them in the projected schedule. You should use the actual date for any milestones that have been met at the time of the report (e.g., submission of study protocol).

When Should Sponsors Submit Post-Approval Study Status Reports?

Unless otherwise specified in the PMA approval order, you should submit a post-approval study status report for medical devices every six (6) months for the first two years and annually thereafter from the date of the PMA approval letter or other negotiated starting dates. This should continue until you have submitted a final study report and we have notified you that you have met the commitment.

You should mark the reports as **6-Month Post-Approval Study Report, Annual Post-Approval Study Report, 18-Month Post-Approval Study Report, 24-Month Post-Approval Study Report**. If you are following a different reporting schedule, you should indicate the appropriate time span on the report cover in bold letters. You should send all reports to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

How Should Sponsors Submit Post-Approval Final Study Reports?

We recommend that you submit the final study report as a separate submission to the PMA. However, you may also submit the final study report as part of the annual report. Your cover letter should prominently identify the submission as **FINAL POST-APPROVAL STUDY REPORT** at the top of the letter and should identify the condition(s) you addressed (i.e., refer to the condition wording and number, if any, used in the approval letter).

How Will CDRH Evaluate Post-Approval Study Interim Reports?

We will evaluate interim post-approval study reports based on a wide range of criteria. Among these are:

- the expected versus the actual progress of the study;
- causes for and solutions to delays in the study progress; and
- adherence to agreed upon methodology and reasons for deviations from the methodology.

We will contact you for clarification if we disagree with your categorization of the status of the study. With this clarification in mind, we will change the status if we believe the data support a different status category.

How Will CDRH Evaluate Post-Approval Final Study Reports?

Your study's final report should describe the study and its results and explain how the study fulfills the post-approval study order. We will review your final report and determine whether or not you have satisfied the post-approval study commitment. If we conclude that you have met the study commitment, you will no longer need to report the status of the study. We will send you a letter informing you that you have satisfied your commitment.

If the final report describes the study but does not fulfill the post-approval study order, you should provide an explanation. There may be legitimate circumstances that make it impossible or inappropriate for the sponsor to complete a particular post-approval study. If we determine that the study cannot be completed as designed but the study objectives remain important, we may terminate the original study and discuss with you establishing a new post-approval study commitment and schedule. If we conclude, however, that you have not met the study commitment required pursuant to 21 C.F.R. 814.82, we may also consider whether other options, e.g., postmarket surveillance under section 522 of the Act, or, in appropriate cases, enforcement actions including civil money penalties, are necessary.

We recommend that you communicate at the earliest possible time with the Center if you intend to terminate the study.

What Post-Approval Study Information will be Available to the Public?

We have often stressed the need to be transparent to our stakeholders, including consumers, physicians, and industry. To accomplish this goal, we intend to publicly post the status of the post-approval studies on our website. We will comply with the requirements of 21 C.F.R. part 20 on the disclosure of information and will not make public any confidential commercial or financial information or trade secrets[3], or any information the disclosure of which might cause an unwarranted invasion of personal privacy.[4]

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[3] 21 C.F.R. 20.61.

[4] See, for example, 21 C.F.R. 20.63(a), "The names or other information which would identify patients or research subjects in any medical or similar report, test, study or other research project shall be deleted before the record is made available for public disclosure."

To make information available to the public, we will post the information on the post-approval studies using an Agency website. The data elements that may be posted are:

- Sponsor Name
- Product name/Proprietary Name(s)
- PMA number
- Annual Report Due Date
- Annual Report Received
- Commitment Description
- Current Status

We will list study commitments on the FDA Internet website for one year following the date of CDRH's letter confirming that the commitment was fulfilled. After that year has passed, we intend to remove the references from the website. This approach is consistent with the FDA policy on CDER and CBER post marketing studies.

Presenting Post-Approval Study Information to CDRH Advisory Panels

We may seek the advice of Advisory Panels when considering the initiation or progress of post-approval studies. These panels are composed of experts outside CDRH who independently review material and make recommendations to us. To assure the Advisory Panel is kept current on the progress of the post-approval studies, we may present or may request that you present the status or outcomes of the studies to the Advisory Panels during their public meetings. Your presentations should contain the information requested in the section of this guidance entitled "What Should the Post-approval Study Status Report Include?" Our presentations will include our analysis and evaluation of the post-approval study.

In summary, this guidance describes how FDA will impose and monitor post-approval studies imposed by PMA order. FDA will generally seek agreement on a protocol before imposing a post-approval study by PMA order. Unless agreement is reached on a different schedule, sponsors should submit status reports containing basic information about the study every six months for the first two years, and annually thereafter. This guidance describes the content of these status reports and CDRH's intention to publish the status of post-approval studies on its web site. Further questions concerning post-approval studies may be directed to Steven H. Chasin, Ph.D., Deputy, Division of Postmarket Surveillance, Office of Surveillance & Biometrics, 301-594-3674.